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HEAD AND NECK

Intensity-modulated radiotherapy in definitive oncological treatment of hypopharyngeal squamous cell carcinoma

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Abstract Hypopharyngeal squamous cell carcinoma (HSCC) is treated by definitive concomitant chemoradiotherapy at most centres. Intensity-modulated radiotherapy (IMRT) is an advanced computer-controlled high-precision radiotherapy technique that has been used at our institution in the treatment of HSCC since 2002. Our aim was to review the treatment results of IMRT-based chemoradiotherapy (CRT) in patients diagnosed with HSCC. The cohort comprised all patients with previously untreated, biopsy-proven squamous cell carcinoma of the hypopharynx treated by definitive CRT using IMRT between March 2002 and November 2010. All patients were diagnosed M0. Forty-five eligible patients were identified. Six patients were treated by radiotherapy alone and 39 patients received concomitant chemotherapy. All patients had a minimum follow-up of 3 years or until death. Complete response was achieved in 29/45 (64 %) patients. Salvage surgery was performed on 10/16 patients with incomplete response. The 5-year estimates for overall survival, disease-specific survival, and local control in the whole cohort were 31, 45, and 64 %, respectively. Classifications T4 and N2c-N3 were prognostic for worse survival. None of the surviving patients needed permanent tracheotomy or PEG tube. We conclude that survival after IMRT-based CRT remained unsatisfactory with frequent relapses at distant sites. The outcome figures were comparable with those that have been achieved by surgery and postoperative radiotherapy. However, all the surviving patients in the current study cohort could retain their functioning larynx. These results using IMRT-based definitive CRT as the primary option for the treatment of HSCC support its continued usage for the delivery of radiotherapy.

Keywords Head and neck squamous cell carcinoma · Hypopharyngeal cancer · Intensity-modulated radiotherapy · IMRT · Chemoradiotherapy

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Introduction

The prognosis of patients with hypopharyngeal squamous cell carcinoma (HSCC) has traditionally been poor. Patients are almost invariably heavy drinkers and smokers and many have significant comorbidities. The majority of patients present with advanced-stage disease and regional and distant metastatic spread of the disease is frequently encountered [1]. Traditionally, best treatment results in HSCC have been reported for surgery and postoperative radiotherapy (RT), which has been regarded as the golden standard in the treatment of HSCC. Disease-specific survival (DSS) figures for this approach in the literature have been 32–56 % [2–5]. Open surgery of HSCC is often mutilating and necessitates removal of the larynx in most cases. In a prospective randomized study by European Organization for Research and Treatment of Cancer (EORTC), published in 1996, larynx could be preserved in 35 % of patients without jeopardizing survival by induction chemotherapy followed by definitive RT for those patients who showed complete response after chemotherapy [6]. After this study and the first reports of high success rates in laryngeal preservation with oncologic treatment

protocols in laryngeal cancer, the justification of primary surgical treatment of HSCC was questioned and a shift in treatment paradigm started to take place in many centres. Larynx preserving concomitant chemoradiotherapy (CRT) at present is the standard of care for HSCC in many centres with surgery as a salvage treatment for patients with treatment failures. However, in the lack of prospective, randomized trials comparing surgery and postoperative RT versus modern, organ-sparing concomitant CRT protocols, there is no universal agreement on the best way to treat HSCC.

In the 1990s, surgery and postoperative RT was most often the treatment of choice for patients with HSCC in Finland [5]. Since 2000 at our institution, the primary treatment for HSCC has been non-surgical in almost all cases. Only, if considered resectable, extensive tumours with seriously affected laryngeal and hypopharyngeal function and/or cartilage destruction are treated by surgery and postoperative RT or CRT.

Intensity-modulated radiotherapy (IMRT) allows production of concave and irregular target volume dose distributions, and thus has the potential to reduce the volume of healthy tissues irradiated to a high dose. In the radiotherapy of head and neck cancer, the RT doses needed for tumour control are often much higher than the tolerance of the surrounding normal structures such as the spinal cord and salivary glands. At the Helsinki University Central Hospital, IMRT has been used in the treatment on head and neck cancer since the year 2000 and is at present the standard RT technique in the treatment of this tumour group. The standard chemotherapy given concomitantly with RT has been cisplatin at dose level of 40 mg/m^2 given once a week during the RT course.

There are only few publications most with relatively small patient series reporting treatment results of IMRT-based RT or concomitant CRT in the definitive treatment of HSCC and some of these studies also include patients with laryngeal cancer [7–10]. The aim of this study was to retrospectively analyse the long-term treatment results of patients treated for HSCC by definitive RT or concomitant CRT using IMRT.

Patients and methods

Patients and tumour characteristics

This retrospective study is a part of the IMRT Quality Assurance Project approved by a Research Ethics Board of the Helsinki University Central Hospital. All patients with previously untreated, biopsy-proven squamous cell carcinoma of the hypopharynx that were treated by definitive RT or CRT using IMRT between March 2002 and November 2010 were enrolled. This period was chosen because the first patient with HSCC was treated by IMRT in March 2002, and only patients with a minimum follow-up time of 3 years or until death were included. IMRT is our standard RT modality in the treatment of head and neck cancer. All HSCC patients treated by this modality were included in this series without any selection. Forty-five patients started the treatment and the results of them all are presented (Figs. 1, 2, 3). All patients had been evaluated by a multidisciplinary tumour board. The hospital records were reviewed and data on patient and tumour characteristics, treatment, and follow-up were collected. There were 39 males and six females. The median age of the patients was 61, range 51–84 years. Pre-treatment evaluation consisted of full medical history, clinical examination, imaging

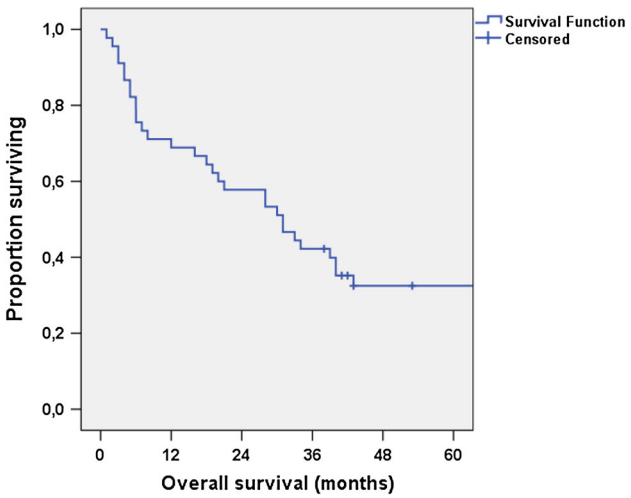

Fig. 1 Overall survival (months) from the end of radiotherapy

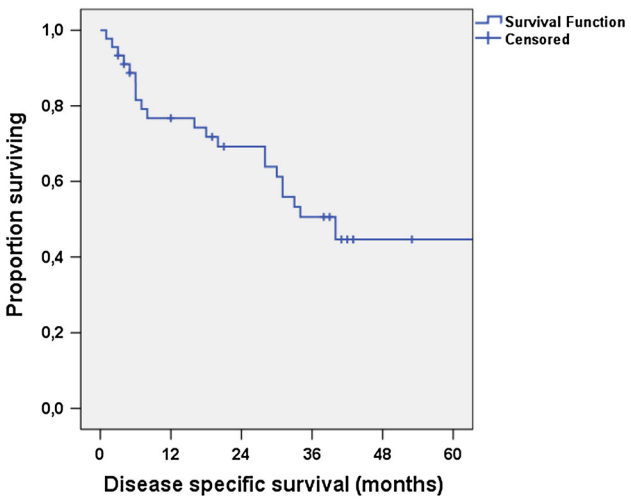

Fig. 2 Disease specific survival (months) from the end of radiotherapy

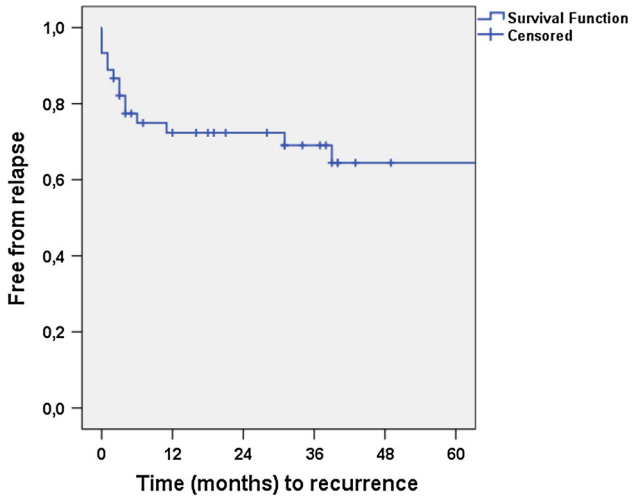

Fig. 3 Local control (months) from the end of radiotherapy

of the primary site and neck by CT or MRI, imaging of the chest and upper abdomen by CT, endoscopy and biopsies under general anaesthesia, and dental evaluation. All patients were staged M0 at presentation. A prophylactic percutaneous endoscopic gastrostomy (PEG) tube was placed in all but one patient. A tracheotomy was performed in 15 patients before the onset of the treatment. The patient and tumour characteristics are presented in Table 1.

Table 1 Patient and tumour characteristics

	n (%)
Sex	
Male	39 (87)
Female	6 (13)
Tumour subsite	
Piriform sinus	39 (87)
Postcricoid	2 (4)
Posterior wall	4 (9)
T classification	
T1	3 (7)
T2	12 (27)
T3	9 (20)
T4a	17 (38)
T4b	4 (9)
N classification	
N0	7 (16)
N1	4 (9)
N2a	5 (11)
N2b	14 (31)
N2c	12 (27)
N3	3 (7)
Stage	
I	1 (2)
II	4 (9)
III	4 (9)
IVa	29 (64)
IVb	7 (16)
Prophylactic PEG tube	
Yes	44 (98)
No	1 (2)
Tracheotomy	
Yes	15 (33)
No	30 (67)

Radiotherapy and concomitant chemotherapy

All patients were treated by IMRT. The patient fixation was done using a thermoplastic mask (Posicast®, Sinmed BV, EM Reenwijk, The Netherlands) until the year 2001, and thereafter a stereotactic head and neck immobilization device (BrainLab®, Heimstetten, Germany) was used. Treatment planning CT was done using a slice thickness of 5.0 mm until the year 2005 and 2.5 mm thereafter. Before the year 2004 the treatment plans were generated with the Cadplan® and thereafter by the Eclipse® (Varian Medical Systems, Palo Alto, CA, USA) treatment planning systems. Irradiation was performed with a 6 MV linear accelerator using a dynamic multileaf collimator (dMLC) and the sliding window principle.

The treatment volume was delineated with the treatment planning CT images and diagnostic CT and/or MRI scans. The clinical target volume first encompassed the primary tumour with a 10 mm margin and the locoregional nodal sites (CTV1). A 5 mm margin was added to the CTV1 to obtain the planning target volume (PTV1). These target volumes were irradiated to a cumulative dose of 50 Gy, given two fractions a day and five fractions a week. After the total dose of 50 Gy the RT was continued to smaller target volumes (CTV2 and CTV3). CTV2 encompassed the primary tumour with 10 mm margin and areas of nodal metastasis and CTV3 the primary tumour and areas of nodal metastasis with closer margins (in average 5 mm) to reduce the areas of healthy normal tissues irradiated to a high dose. The mean total dose of RT was 69.6 Gy (range 58–70 Gy) and the mean total treatment time 51 days (range 37–66 days).

The standard oncological treatment for HSCC at our institution is CRT consisting on IMRT and weekly cisplatin 40 mg/m^2 given concomitantly with RT. In the present series, six patients were treated by RT alone because chemotherapy was considered to be contraindicated on the basis of existing comorbidities. Thirty-nine patients received concomitant chemotherapy. In 37 patients this consisted of cisplatin 40 mg/m^2 scheduled to be given once a week up to six cycles during the RT. Two patients

received concomitant mitomycin at the dose 10 mg/m^2 given once during the RT.

Assessment of treatment response and follow-up protocol

The otolaryngologist—head and neck surgeon made the first clinical assessment of treatment response approximately 1 month after cessation of treatment. To further examine the treatment response, CT, MRI, or since 2007 uniformly positron emission tomography–CT (PET–CT) was scheduled 3 months after completion of the treatment. Biopsies were taken in cases suspicious for residual disease. In 29 patients the treatment response was assessed to be complete with no clinical or radiological evidence of residual tumour. No further treatment was offered for these patients except for one with N2a neck disease, who had planned neck dissection performed. In 16 patients the treatment response was assessed as incomplete: in three cases local, in 10 regional, and in three local and regional residual disease was suspected. Salvage surgery was performed on 10 of these patients consisting of neck dissection in seven patients and laryngopharyngectomy, neck dissection and reconstruction in three patients. In one patient a neck dissection was performed for palliative purposes because of large residual tumour in the neck. The reasons for not performing surgery in five patients were: patient refusal ($n = 1$), distant metastasis ($n = 2$), poor patient condition ($n = 1$), and inoperable disease ($n = 1$). Therefore, in six patients complete remission of the disease was not achieved at any stage.

PEG tube removal was indicated when the patient had returned to full oral feeding and did not need the tube any longer with the exception of planned salvage surgery with assumed need for postoperative tube feeding.

During the first year of the follow-up, the patients were seen every 2–3 months, then during the second year every 3–4 months, and thereafter every 4–6 months. According to our national protocol, the follow-up is continued until 5 years from the completion of treatment or the last episode of recurrent disease.

Statistical analysis

The SPSS statistical program (version 17.0, Chicago, IL, USA) was used for statistical calculations. Survival was estimated using the Kaplan–Meier product-limit method. Cox regression analysis was used to calculate the significance of patient and tumour characteristics on local control and survival. p-values less than 0.05 were considered statistically significant. Local recurrence-free survival (LC) was calculated from the date of RT completion to the date of first locoregional recurrence or death, censoring patients alive without local recurrence on the last date of follow-up. Local control was defined as absence of primary tumour and regional nodal metastasis at physical examination, endoscopy and imaging. Overall survival (OS) was calculated from the last date of RT to the date of death. Disease-specific survival (DSS) was calculated from the last date of RT to death caused by HSCC. The predictive value of tumour characteristics on development of distant metastasis was calculated by Cox regression analysis. In this analysis, the survival was calculated from the last day of RT to the date of detection of distant metastasis.

Results

Local control, survival and patterns of relapse

The minimum follow-up time was 36 months or until death (range 36–136, mean 74).

During the study period, 31 out of the 45 patients died. Twenty-two patients died of the index disease and nine patients of other causes. The 5-year estimates for OS, DSS, and LC were 31, 45, and 64 %, respectively.

Thirty-nine patients were regarded as free of disease after initial treatment consisting of RT or CRT and in 10 cases also salvage surgery. In 18 out of these patients (46 %) tumour recurrence was detected in further follow-up; four patients developed a locoregional recurrence, four patients both locoregional and distant recurrence, and in 10 patients tumour recurred at distant site only. Therefore, in 14 out of 18 cases (78 %) the tumour recurrence involved distant metastasis. No further operations were made for these recurrences and all these 18 patients have died. Lung was the most frequent site for distant metastasis ($n = 13$), followed by liver ($n = 2$), and mediastinum ($n = 2$). Distant metastasis was detected more often in patients with advanced nodal or tumour stage. In patients with N0–N2b nodal disease distant metastasis occurred in 23 % of patients (7/30) and in patients with N2c–N3 nodal stage in 47 % of patients (7/15) ($p = 0.07$). In T3–T4 tumours there was also a tendency towards more metastatic disease versus T1–T2 tumours. This difference did not, however, reach statistical significance ($p = 0.23$).

In the cohort of patients with complete response, 17 out of 29 patients (59 %) died (nine of HSCC). Fourteen out of the 16 patients (88 %) with incomplete response to RT or CRT died (13 of HSCC), despite salvage surgery was attempted in 10 patients consisting of laryngopharyngectomy in three patients and neck dissection only in seven patients. All three patients who had laryngopharyngectomy performed died within 18 months because of recurrent disease. Two out of the seven patients who had only neck dissection performed survived.

Older age was found to be a significant poor prognostic marker for LC and OS ($p = 0.04$ and 0.01, respectively), whereas gender did not affect the treatment result. Tumour-related factors that were found to have significant prognostic value were tumour and nodal classification. In patients with a T1–T3 tumour, LC (87 vs. 39 %, $p = 0.08$), DSS (63 vs. 26 %, $p = 0.02$), and OS (35 vs. 21 %, $p = 0.05$) were better than in patients with T4 tumours. Prognosis was also better in patients with nodal stage N0–N2b versus those with N2c–N3 (LC 87 vs. 50 % $p = 0.005$, DSS 59 vs. 23 %, $p = 0.02$, and OS 47 vs. 7 %, $p = 0.02$).

The prognosis was poor in patients ($n = 8$) that were not fit for standard therapy consisting of RT with concomitant cisplatin. Only one of these patients survived.

Four patients developed second primary tumours in the follow-up. Two patients were operated for a second primary pulmonary carcinoma. In one patient, a liposarcoma of thigh was operated and one patient got RT for oesophageal carcinoma but finally succumbed because of it.

PEG and tracheotomy dependency and osteoradionecrosis

A prophylactic PEG tube was placed in 44 patients (98 %). In one case, the tube had to be removed soon after insertion because of infection. In one case, the tube detached before the end of the treatment. No new tube was inserted for these two patients. PEG tube could be removed from 34 out of the remaining 42 patients (81 %) having PEG tube in place through RT or CRT. Mean period from the completion of the RT or CRT to PEG removal was 114 days (3.8 months), range 6–456 days (0.2–15.2 months). The PEG tube was not removed from eight patients (19 %), seven out of which died of their index disease and one committed a suicide before PEG removal. Therefore, there were no survivors with PEG dependence. Mean period living with the PEG tube after completion of the RT or CRT in these eight patients was 271 days (9.0 months), range 68–610 days (2.3–20.3 months). In all 42 patients, the mean period with PEG tube in place after completion of the RT or CRT was 139 days (4.6 months), range 6–610 days (0.2–20.3 months). Four patients had PEG tube in place at 1 year and none of the patients at 2 years after treatment.

Fifteen patients had tracheotomy during RT or CRT. Eleven out of these patients were later decannulated. Two patients had laryngopharyngectomy performed and two had tracheotomy until death. Therefore, none of the surviving patients needed permanent tracheotomy.

One patient developed serious osteoradionecrosis of mandible resulting eventually in mandibular resection and reconstruction 2.5 years after completion of CRT.

Discussion

To our knowledge, with 45 patients and mean follow-up time of 74 months, this is the second largest patient series with the longest follow-up time consisting solely of patients who had IMRT-based definitive RT or CRT for HSCC. We retrospectively analysed the outcome of 45 patients who had been treated between March 2002 and November 2010 with minimum follow-up time of 3 years for surviving patients. This series represents a population-based cohort as all patients with HSCC in the referral area covering approximately 1.6 M people have been treated at our institution. The 5-year estimates for OS and DSS were 31 and 45 %, respectively. This compares favourably to corresponding figures reported for surgery and postoperative RT [2–5]. In a study by Laranne et al. [5] reviewing HSCC in Finland between 1990 and 1999, the 5-year DSS for patients treated by surgery and postoperative RT was 32 %, and for those treated with concomitant CRT 38 % corresponding well to the current results, although it must be noted that the number of patients in the CRT arm was small ($n = 12$). The survival figures being close to equal there seems to be little doubt about the preferable treatment for HSCC, considering that all the surviving patients in the present study could retain their larynx. Moreover, none of the surviving patients in our study cohort had permanent PEG tube or tracheotomy indicating that in all cases the preserved larynx was functioning reasonably well.

During the last decade IMRT has in most western institutions become the standard RT technique in the treatment of head and neck cancer. In HSCC the primary tumour is often of advanced size and in most cases also nodal metastasis is present at diagnosis. The ability of IMRT to produce highly conformal RT dose distributions enables to achieve good dose coverage at primary tumour site and at the site of nodal metastases with simultaneous sparing of normal structures such as spinal cord, parotid glands, mandible and oral mucosa. In a study by Al-Mamgami et al. [11] IMRT was compared with normal three-dimensional conformal radiotherapy (3D-RT) in the treatment of HSCC and it was found to reduce the incidence and severity of treatment related acute and late toxicity. The locoregional control rates following IMRT combined with concurrent chemotherapy have also been found to be encouraging [7, 9, 12]. The number of patients in most series published so far is, however, small and in some series also patients with laryngeal cancer are included. In the largest and most recent series consisting of 91 HSCC patients treated with IMRT and 90 with 3D-RT, IMRT resulted in better LC (75 vs. 58 %) but there was no difference in OS (50 vs. 52 %) or distant relapse rate (23 vs. 20 %) at 3 years compared with patients treated with 3D-RT [10].

The results of salvage surgery were dismal. After clinical and radiological assessment of treatment response, 16 patients were assessed to have incomplete response to oncological treatment. Despite attempts of surgical salvage in 10 cases only two patients in this cohort survived; 13 patients succumbed because of HSCC and one for other reason. This finding equals well with other studies, in which the prognosis of non-responders to CRT has been poor in patients treated for head and neck squamous cell carcinoma [13, 14].

There does not seem to be many survivors among patients with initially complete response who will develop tumour recurrence in the follow-up. Of the 39 patients who were thought to be free of disease after their initial treatment in our study cohort, 18 patients later developed a recurrence. In strikingly many cases the recurrence involved distant sites (78 %). All these 18 patients succumbed to the consequences of HSCC.

A hypopharyngeal primary site has been shown to be predictive of a need for feeding tube during CRT and also predictive of later hypopharyngeal stricture formation [15]. Using meticulous target delineation allowed by IMRT it is possible to decrease the radiation dose to pharyngeal constrictor muscles. It has been our policy to place prophylactic PEG tube for all patients undergoing CRT for HSCC. In the current study cohort all but one patient had PEG tube inserted before the treatment. Four patients were having PEG tube in place 1 year after cessation of the treatment and none at 2 years. In the study by Mok et al., four of the 91 IMRT treated patients were having PEG tube in place at 2 years and there was no difference in 2-year PEG dependency rate between the IMRT and the 3D-RT groups [10]. In a study by Al-Mamgani et al. [11], IMRT was found to reduce PEG dependency at the end of treatment for HSCC as compared with conventional radiation technique.

The prognosis of patients with HSCC remains unsatisfactory. However, we can demonstrate progress that has been achieved in the treatment of HSCC patients in Finland. Kajanti et al. [16] reported the treatment results of HSCC patients treated at our institution during the years 1958–1982. In this study, 135 patients were treated with curative intent, of which 106 were given radical RT and 29 were treated with surgery and postoperative RT. The 5-year OS figures for these patient cohorts were 16 and 28 % and for all patients treated with curative intent 18 %. In a study by Laranne et al. [5], HSCC patients treated at the five university hospitals in Finland during the years 1990–1999 were reviewed. Of the patients in this material who were treated with curative intent, 64 were operated and radiated postoperatively, 33 were treated with definitive RT, and 12 with concomitant CRT. The 5-year DSS estimates for these groups were 32, 7, and 38 %, respectively, and for all the patients treated with curative intent 27 %. During the years covered by the present study, the treatment of choice for HSCC has been definitive RT or CRT using IMRT. Therefore, practically all HSCC patients treated with curative intent at our institution during this period are included in this study. The 5-year estimates for OS and DSS have improved being 31 and 45 %, respectively, in the current study. Furthermore, a major improvement for the surviving patients is the preservation of functioning larynx. In addition, it has been shown that in the treatment of HSCC, the late radiation-induced xerostomia is less disturbing after IMRT than after conventional RT [11].

In conclusion, the prognosis of HSCC after IMRT-based RT or concomitant CRT remained unsatisfactory with frequent relapses at distant sites. However, the outcome figures were comparable with those achieved by surgery and postoperative RT. A major advantage over surgical approach was the preservation of functioning larynx of all the surviving patients in the current study cohort. Our results using IMRT-based definitive CRT as the primary option for the treatment of HSCC support its continued usage for the delivery of radiotherapy.

Conflict of interest None declared.

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